REMARKS

Reconsideration and withdrawal of the rejections of the application are respectfully requested in view of the amendments and remarks herewith, which place the application into condition for allowance. The Examiner is thanked for courtesies extended during the July 9, 2003 telephonic interview.

I. STATUS OF CLAIMS AND FORMAL MATTERS

Claims 1, 5, 6, 9-11, 14-17, 21, 22, 24, 47, 49-51, 53-55 and 57-79 are pending in this application. Claims 1, 5, 6, 14-16, 21, 22, 24, 47, 50, 54, 55, 57 and 58 are currently amended; claims 60-79 have been added to round out the scope of protection to which Applicants are entitled. For the Examiner's convenience, a clean copy of the pending claims is appended.

It is submitted that the claims, herewith and as originally presented, are patentably distinct over the prior art cited by the Examiner, and that these claims were in full compliance with the requirements of 35 U.S.C. §112. The amendments of and additions to the claims, as presented herein, are not made for purposes of patentability within the meaning of 35 U.S.C. §§§§ 101, 102, 103 or 112. Rather, these amendments and additions are made simply for clarification and to round out the scope of protection to which Applicants are entitled. Furthermore, it is explicitly stated that the herewith amendments should not give rise to any estoppel, as the herewith amendments are not narrowing amendments.

Support for Amended and Newly Added Claims

Claim 1: Support for a functional splice donor site within the 5' LTR can be found in Figure 27c, which depicts the splice donor site (SD) within the 5' LTR. Also depicted in Figure 27c is the position of the second nucleotide of interest (NOI) downstream of the splice acceptor site and upstream of the 3' LTR. Support for the recitation "whereby the first NOI is removed as a result of splicing" can be found on page 30, lines 31-32, where the intervening sequence between the SD and the splice acceptor site (SA) is removed as a result of splicing.

Claim 47: Support for "a packaging cell" can be found in the last paragraph of page 47 and the first paragraph of page 48, where packaging cells are described. Packaging cell lines are also discussed in the paragraph bridging pages 11 and 12 of the specification; and, the structure of one pro-vector, as it would be in the packaging cell, is shown in Figure 17. Further, the term is standard in the art, as is demonstrated by the attached pages from the Clontech catalog, describing several commercially available packaging cell lines. "Target cell" is defined on page

46, lines 17-18, and is synonymous with the "transduced cell" referred to in Figure 17, in which splicing occurs.

Claim 55: Support for the addition of "heterologous" can be found in the paragraph beginning on page 83, line 27, wherein a heterologous transcriptional control sequence (e.g. a promoter) is discussed in relation to the expression of lentiviral components.

Claim 57: Support for the language regarding removal of the intervening sequence can be found on page 30, lines 31-32, where such removal is depicted.

Claims 60: Support for the use of an internal promoter can be found in the paragraph beginning on page 16, line 9.

Claims 61 and 62: Support for a heterologous transcriptional control element in an LTR can be found in Figures 6, 9 and 10, where the CMV promoter is present in an LTR. Further support can be found in Figure 17, where the pro-vector contains a CMV promoter in its 5' LTR and a hypoxia responsive promoter in its 3' LTR, and where the vector, after reverse transcription, contains a hypoxia responsive promoter in each LTR.

Claims 63, 64, 65, 66, 67, 68, 69, 70, 71, 72 and 73 depend from claim 57 and mirror claims 50, 51, 9, 10, 11, 14, 15, 16, 17, 21 and 22, respectively.

Claim 74 is a method for producing the vector of claim 57. The language of claim 74 mirrors that of claim 47.

Claims 75, 76, 77, 78 and 79 depend from claim 74 and mirror claims 55, 60, 61, 62 and 59, respectively.

The remaining claim amendments are stylistic and place the claims in better form.

No new matter is added.

Corrections to Drawings

Inadvertent typographical errors have been discovered in Figures 17 and 27c. Pursuant to 37 C.F.R. §1.121, attached are copies of Figures 17 and 27c, showing the proposed changes marked in red. Also attached are clean copies of the corrected drawings, in anticipation of the Examiner approving the changes. The amendments to the drawings are simply to correct typographical errors, and do not constitute new matter.

II. THE OBJECTIONS TO THE CLAIMS ARE OVERCOME

The components of claim 1 have been re-itemized, as suggested in the Office Action. The quotation marks have also been deleted.

It is respectfully submitted that claims 58 and 59 are written correctly. Although they refer to other claims, they are not dependent claims in the strictest sense. Claim 58 is directed to a retroviral particle, whereas the claim to which it refers, claim 57, is directed to a retroviral vector. Therefore, the change suggested in the Office Action would render claim 58 indefinite for lack of antecedent basis. Claim 59 is a product by process claim, and thus properly begins with "a" rather than "the".

Claim 24 has been amended to recite "the retroviral vector", rather than "a retroviral vector", as suggested in the Office Action.

The word "tile" in claim 47 was a typographical error, and has been changed to "the".

Reconsideration and withdrawal of the claim objections are requested.

III. THE REJECTIONS UNDER 35 U.S.C. §112, 1ST PARAGRAPH ARE OVERCOME

The Application Contains Adequate Written Description

Claims 1, 5, 6, 9-11, 14-17, 21, 22, 24, 30 and 46-59 were rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking adequate written description. The rejections are traversed.

The Office Action argues that the specification does not provide support for a splice donor site (SD) within a 5' LTR. As discussed above and during the telephonic interview on July 8, 2003, a SD within a 5' LTR is depicted in Figure 27c.

The Office Action goes on to state that the specification does not provide support for the vector of claim 1. The Examiner's attention is again respectfully directed to Figure 27c, which shows a vector with (a) a 3' and 5' LTR; (b) a functional SD within the 5' LTR; (c) a functional splice acceptor site (SA); (d) a first nucleotide sequence of interest (NOI) flanked upstream by the functional splice donor site and downstream by the functional splice acceptor site (in Figure 27c, this is depicted as "Selectable gene"); and (e) a second NOI downstream of the functional splice acceptor site and upstream of the 3' LTR (in Figure 27c, this is depicted as "NOI 2"). As is indicated on page 67, lines 20 and 21, Figure 27c is representative of an embodiment of the instant invention. Therefore, claim 1 is not new matter, but is found schematically represented in the application as Figure 27c.

The language of claim 5 has been amended to clarify that what is claimed is an expression product of the retroviral vector of claim 1. This is not new matter, as the Office Action admits that the specification supports an NOI (such as the second NOI recited in part (e) of claim 1) encoding a protein that is a therapeutic or diagnostic agent.

The Office Action alleged that the limitations in claims 15-17 describing the source of the SA are new matter. Applicants apologize for any confusion caused by inadequate indication of support for these claims, and hope that the following explanation clarifies the support for claims 15-17. The paragraph beginning on page 25, line 4, defines a first nucleotide sequence (NS) as one that is "capable of yielding a functional splice donor site" and a second NS as one that is "capable of yielding a functional splice acceptor site". Therefore, the first NS corresponds to the nucleotide sequence containing the functional SD, and the second NS corresponds to the nucleotide sequence containing the functional SA. In the paragraph beginning on page 25, line 28, the second NS (*i.e.*, the SA) encodes an immunological molecule or part thereof. Subsequent paragraphs identify aspects of the invention wherein the immunological molecule is an immunoglobulin, or wherein the second NS (*i.e.*, the SA) encodes an immunoglobulin heavy chain variable region. Therefore, according to pages 25 and 26 of the specification, the SA can be derived from a nucleotide sequence encoding all or part of an immunological molecule, *e.g.*, an immunoglobulin or immunoglobulin heavy chain variable region, which is what is claimed in claims 15-17. Thus, these claims do not constitute new matter.

Claims 22 and 54 have been amended to recite "HIV-1", rather than "HIV", obviating the rejection on that basis.

Claim 46 has been cancelled, rendering the new matter rejection with respect to that claim moot.

Claim 47 is not new matter; rather, it is a method of making the vector of claim 1, which, as discussed above, is also not new matter. The Examiner's attention is again respectfully directed to Figure 27c, wherein the starting material, *i.e.*, the pro-viral vector having an SD within the 3' LTR, is depicted in the first diagram. In fact, the pro-vector in Figure 27c contains (i) a 3' and 5' LTR; (ii) a functional SD located within the 3' LTR; (iii) a functional SA upstream of the SD; (iv) a first NOI upstream of the functional SA (indicated as "Selectable gene"); and (v) a second NOI downstream of the functional SA (indicated as "NOI 2"), exactly as claimed in part (a) of claim 47. Further support for an SD in the 3' LTR can be found in Figure 2 and in its legend (page 68, lines 5-10), and in Example 1, wherein a plasmid having an SD between the U3 and R of the 3' LTR. This plasmid forms the basis for the construction of the pICUT vectors, which, upon reverse transcription, generate the claimed retroviral vectors of the invention.

The process for producing a retroviral vector, for example, from the starting material described in claim 47(a) is taught in the paragraph bridging pages 11 and 12 of the specification, *i.e.*, a retroviral vector is produced in a target cell. The general process of reverse transcription of virion RNA (*e.g.* a retroviral pro-vector) into a transcript (*e.g.* a retroviral vector) is both depicted and explained on page 5 of the specification. Generation of a retroviral vector from a retroviral pro-vector by reverse transcription is also discussed on page 29, lines 23-24 of the application. For clarity, the language of claim 47 has been amended to recite a "packaging cell" and a "target cell".

Claim 49 has also been amended to recite a "packaging cell". As discussed above, there is support in the specification for this recitation. On page 25, lines 20-22, the aspect of the invention that is claimed in claim 49 is described, *i.e.*, the first NOI is expressed at a "primary target site". As defined on page 46, a "primary target site" is the first site a vector is capable of transfecting or transducing. In this instance, the primary target site is the packaging cell.

Claim 51 finds support in the same section of the specification, which teaches that the first NOI can be a viral element. The paragraph beginning on page 33, line 23 states that the first NOI can contain a packaging signal. The following paragraph, being on page 33, line 28, states that the first NOI can contain an *env* sequence. Combinations of viral elements are contemplated on page 30, lines 9-10. Therefore, claim 51 does not include new matter.

Claim 52 has been cancelled, obviating the new matter rejection of that claim.

With respect to claim 55, there are several places in the application wherein a heterologous transcriptional control element is disclosed. As was previously pointed out, the transcriptional control element itself is taught on page 30, lines 16-18. Its location can be ascertained by the preferred embodiment disclosed in line 16, *i.e.*, the U3 region. This is perhaps best visualized by comparing the provirus depicted on page 5 with the pro-vector of Figure 27c. The LTRs shown on page 5, are comprised of a U3, R and U5 region, in that order. Comparing that diagram to the location of the SD in Figure 27c, one can see that the U3 region is upstream of the SD in the pro-vector. Further, internal promoters are discussed in the paragraph beginning on page 16, line 9, of the specification, teaching that the transcriptional control element need not be located in the LTR. The concept of claim 55 is also schematized in Figure 17, where both a CMV promoter and a hypoxia responsive promoter are located upstream of the SD on the pro-vector.

An LTR is understood, in general terms, by one of skill in the art, to be a terminal sequence that has the capacity of being repeated upon reverse transcription. Modification of LTR sequences was well known in the art at the time the invention was made. *See* Cannon *et al.* J. Virol. 70(11): 8234-8240 (Nov. 1996), attached. Cannon *et al.* teach that the skilled artisan knew that the CMV promoter could functionally replace the U3 region of the 5'LTR in the plasmid DNA. Furthermore, Cannon *et al.* teach that hybrid LTRs were functionally equivalent to wild-type LTRs upon reverse transcription. *See* Figure 1, page 8235. Cannon *et al.* conclude, on page 8239, that "as the minimum sequence requirements for LTR function are further defined, it will be possible to construct completely synthetic LTRs containing transcriptional and translational control features designed to give specific gene expression characteristics." Therefore, an LTR was understood by one of skill in the art, at the time of the invention, to encompass modified LTRs.

As noted above, the invention contemplates LTRs that are altered by deletion and/or substitution. The instant invention can include retroviral vectors with an altered enhancer/promoter region of the LTR, as is suggested on page 15, lines 17-18, of the application. The LTRs included in the vectors of the invention can also be at least part of a 5' LTR and/or at least part of a 3' LTR, as discussed on page 40, lines 4-7. As such, and as discussed above, the U3 region modification with a promoter such as the CMV promoter is embodied in the invention. *See also* Figure 18, which demonstrates modification of the U3 region to include sequences of the coding region of a gene of interest.

Claim 56 has been cancelled, obviating the new matter rejection of that claim.

For reasons discussed with respect to claim 1, claim 57 is not new matter. Figure 27c shows a vector comprising (a) a 3' and 5' LTR; (b) a functional splice donor site located with the 5' LTR; (c) a functional splice acceptor site located downstream of the functional splice donor site; and (d) an NOI downstream of the functional splice acceptor site and upstream of the 3' LTR, as claimed in claim 57. Removal of an intervening sequence between the SD and SA by splicing is shown on page 31. Another depiction of this embodiment is set forth in Figure 12: the intervening sequence between the SD and SA comprises a packaging signal (PSI) and there is an NOI downstream of the SA. Upon reverse transcription, the intervening sequence comprising the packaging signal is spliced out. *See also* the paragraph bridging pages 69-70, and page 33, line 23, of the specification.

Applicants regret any confusion that may have resulted from incomplete or extraneous support provided previously for added and/or amended claims.

The Claims Are Enabled

Claims 1, 5, 6, 9-11, 14-17, 21, 22, 24, 30 and 46-59 were rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking enablement. The rejections are traversed.

A brief summary of the invention may be useful for the enablement discussion to follow. The instant invention is a retroviral vector for the transfer of a nucleic acid or multiple nucleic acids to a target cell. The features of the vector include 5' and 3' LTRs flanking each end of the vector, and engineered splice donor and splice acceptor sites between the LTRs. The LTRs can play a role in transcriptional control; they also are essential for vector integration into the genome of the target cell.

Production of a suitable retroviral vector is a multi-step process. First, a pro-vector containing the desired elements, in this case, a 5' and 3' LTR, an SA, at least one NOI downstream of the SA, and an SD located in the 3' LTR, is constructed and transferred into cells that will package the pro-vector into a viral particle (called "packaging cells" in this application). The pro-vector can contain any number of NOIs, all of which are capable of being used/expressed in the packaging cell.

A target cell is infected with the viral particle made by the packaging cell, and the pro-vector is reverse-transcribed. This process results in duplication of the LTRs at opposite ends of the molecule, due to the mechanism of the reverse transcriptase enzyme. As such, the SD that was located in the 3' LTR of the pro-vector (and therefore downstream of the SA), is now also located in the 5' LTR, upstream of the SA, in the vector. Splicing can only occur when the SD is upstream of the SA, which is why the pro-vector is not spliced, but the vector is spliced.

Because the pro-vector is not spliced, all sequences it contains are available for use, *i.e.*, a first NOI upstream of the SA in the pro-vector can be expressed, if it is a coding sequence, or can otherwise function, for example, as a packaging sequence. For safety reasons, such a sequence may be undesirable for use in subjects. The instant invention provides a vector that overcomes this problem by supplying an SD and SA that flank the first NOI, thereby facilitating its removal by splicing of the vector. The spliced vector retains the NOI that is downstream of the SA ("the second NOI" in one embodiment), and can deliver that NOI to another cell. Using this process,

large quantities of a vector for gene delivery, without extraneous viral elements or selectable marker genes, can be produced in the target cells for purification and use in subjects.

The Office Action argues, on page 9, that the use of any NOI would be unpredictable, since it is unknown which NOIs might contain cryptic splice sites. This assertion appears to rest on the assumption that the identification of splice sites requires undue experimentation, which is not the case. SD and SA sequences are, and have been, well known in the art for quite some time. Attached is a section of "Genes VI", by Benjamin Lewin (1997, Oxford University Press, Inc. New York), considered by many to be the preeminent molecular biology text, which discusses splice donor and acceptor sites. As taught in Lewin, the consensus sequence at each splice site is known and identifiable. This is further demonstrated by the four pre-filing references previously submitted with the January 2, 2002 Amendment and with the April 3, 2002 RCE (Sebillon *et al.*, Maruyama *et al.*, Burn *et al.*, and Reichel *et al.*). A brief discussion of each reference follows.

Sebillon *et al.* deals broadly with splicing of the human β-globin gene. More specifically, they identified a mutation in the SA site of the second intron in a patient with β-thalassemia intermedia. On page 3419, column 2, the authors discuss how mutations in splice sites, particularly in the GU-AG consensus region, have been associated with several genetic diseases. They also point out that 101 such mutations had been identified by the publication date of 1995. Sebillon *et al.* go on to teach assays to detect splicing patterns and identify spliced products (page 3420, column 1, "RNA transcription and splicing"), thereby characterizing the splice site mutation in their patient.

Maruyama *et al.* is similar to Sebillon *et al.* in that it characterizes splice site mutations in patients with a genetic disorder, in this case, familial hypercholesterolemia. Maruyama *et al.* describe how to use routine molecular biology tools and techniques, such as PCR and restriction analysis, to identify transcripts of the gene encoding the LDL receptor. Table 1 (page 703) shows the nucleotide sequences of the normal, mutant and cryptic 5' (donor) splice sites. Table 1 is explained on page 705, column 1, second full paragraph, where the authors also describe how they searched for and identified cryptic splice sites.

Burn *et al.* also teach how to find and identify cryptic splice sites, particularly in the section of the reference beginning on page 184, column 1, under **(a) The pSPL3 splicing vector contains a cryptic exon**. The first paragraph of that section describes how to identify and characterize the cryptic site, and the next paragraph (and Figure 2) teaches how to remove it.

Reichel *et al.* describe the removal of a cryptic splice site in the gene encoding green fluorescent protein (GFP). The Examiner's attention is particularly directed to page 5889, column 1, lines 20-26, where the construction of plasmid pCK GFP 10, including removal of a cryptic splice site that was previously recognized by other investigators, is described. This modification was necessary for the expression of GFP in transformed plants, as is discussed in the paragraph bridging pages 5889 and 5890.

These four references unambiguously demonstrate that, at the time the current application was filed, it was a routine procedure for the skilled artisan to identify and remove cryptic splice sites from transcripts of interest. Turning to the application, Figure 27c acknowledges the possibility that cryptic splice sites may be encountered in the vectors of the invention. (Figures 27a and 27b also acknowledge that cryptic sites may be present in wild type and previously known retroviral vectors.) It should be noted that not every NOI will have a cryptic site; in fact, most will not. However, one of skill in the art would know that a cryptic splice site is likely to be present if no or incomplete expression of the NOI is observed. S/he would then use the routine molecular biology procedures described in Sebillon *et al.*, Maruyama *et al.*, Burn *et al.*, Reichel *et al.*, or a variety of other sources to eliminate the cryptic splice site such that the NOI is properly expressed. This does not represent undue experimentation on the part of the skilled artisan. It should further be noted that the presence of a cryptic splice site is only relevant to the claimed invention if it appears in an NOI placed upstream of the splice acceptor upon transduction. As such, an NOI having a cryptic splice site that occurs downstream of the splice acceptor is not subject to a splicing event, and has no bearing on the vectors of the invention.

Further, it is well settled law that a patent application need not teach, and preferably omits, what is well known in the art. *See, e.g., Spectra-Physics, Inc. v. Coherent, Inc.*, 827 F.2d 1524, 3 USPQ2d 1737 (Fed. Cir. 1987). That is, a patent application need only begin teaching where the art leaves off, and a patent application need not teach that which is known in the art. The references discussed above were available at the time the instant application was filed, and the information contained in them should, therefore, not be restated in the current specification, particularly given the fact that many NOIs do not contain cryptic splice sites.

Although it is earnestly asserted that the claims were enabled, functional language has been added to claims 1 and 57, specifying that the sequence between the SD and SA (*i.e.*, the

first NOI in claim 1 and the intervening sequence in claim 57) is spliced out. This language excludes the possibility of errant splicing due to cryptic sites.

The Office Action states, on pages 9 and 10, that the specification does not enable making the retroviral vector claimed by mere reverse transcription, that the essential elements describing the structure and function of the vector and pro-vector are not in the claims, and that the steps required to make the vector are not in the claims. Applicants disagree.

Firstly, the suggestion that the translocation of the SD to a position upstream of the SA during reverse transcription should be recited in the claims is akin to suggesting that a claim reciting "wherein the nucleic acid is expressed" should also recite that a ribosome binds to an mRNA and that peptidyl transferase enzymes facilitates the addition of amino acids to a growing polypeptide chain. Just as the skilled artisan understands how protein expression works, so does s/he understand how reverse transcription works.

Secondly, integration of the pro-virus into the host cell's genome does not result in addition of an intron, as is stated on page 9 of the Office Action. The Office Action goes on to assert that no protein will be expressed because the gene of interest is in the intron, that expression of a second gene of interest is activated because of the functioning intron, and that the first NOI has no function if (1) there is no second NOI and (2) it is not within an intron. It is hoped that the following explanation of the invention clears up these misconceptions.

A pro-vector, containing (i) a 3' and 5' LTR; (ii) a functional SD located within the 3' LTR; (iii) a functional SA upstream of the splice donor site; (iv) a first NOI upstream of the functional SA; and (v) a second NOI downstream of the functional SA and upstream of the 3' LTR, as recited in claim 47, is made and transfected into a packaging cell, where it is packaged into a viral particle. When it is introduced into the packaging cell, the pro-vector already contains the components listed above. No additional intron is introduced as a result of integration into the packaging cell's genome.

Depending upon what transcriptional control elements are also present in the pro-vector, expression of the first and second NOI may be controlled simultaneously by elements in the 5' LTR, or they may be controlled separately by the presence of one or more internal elements (*e.g.* an internal promoter). The expression of one NOI is not dependent upon the expression of the other NOI.

Finally, in the pro-vector, which is the subject of claim 47(a), the first NOI is not in an intron. (See Figure 27c.) The first NOI is only in an intron after reverse transcription of the pro-vector has occurred and the SD is copied into the 5' LTR. At that point, the first NOI is located between the SD and the SA, and is thus spliced out. In the pro-vector, there is no SD located upstream of the first NOI, and it can be expressed or otherwise function as intended (*e.g.*, as a packaging signal).

The steps of claim 47 accurately reflect the process of making the vector of the invention; and, as discussed in previous sections of this Amendment, the method of claim 47 is adequately described and supported by the specification.

Claim 5 was rejected because the specification is allegedly not enabling for therapy or diagnosis. Claim 5 essentially claims an expression product of the vector of the invention, not a method of treating or diagnosing. As it is well-known in the art how to obtain an expression product from a given vector, such as the vector of the instant invention, it is submitted that claim 5 is enabled by the specification.

In view of the foregoing, reconsideration and withdrawal of the 35 U.S.C. §112, first paragraph, rejections are requested.

IV. THE REJECTIONS UNDER 35 U.S.C. §112, 2ND PARAGRAPH ARE OVERCOME

Claims 1, 5, 6, 9-11, 14-17, 21, 22, 24, 30 and 46-59 were rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite. The rejections are traversed.

Claim 1 has been amended to clarify that the second NOI is upstream of the 3' LTR. The language of claim 1 makes clear the relationship of the vector components to one another. For instance, the 5' LTR is obviously at the 5' end, and the 3' LTR is obviously at the 3' end. The SD is within the 5' LTR; there is a first NOI between the SD and SA; and there is a second NOI between the SA and the 3' LTR. Therefore, claim 1 is not indefinite.

Claim 5 has been amended to clarify that the second NOI encodes a therapeutic or diagnostic expression product.

Claim 6 has been amended to remove the recitation "or a combination thereof", which simplifies the language. Claim 6 is clearly directed to a vector wherein the first NOI itself is or encodes a viral element (*e.g.* a packaging sequence or Env) or wherein the first NOI encodes a selectable marker.

The language of claim 14 has been rearranged to clarify that the vector of claim 1 further comprises a multiple cloning site (MCS) downstream of the SA. The presence of a MCS allows for the insertion of additional NOIs, but a recitation of its function is not necessary to render claim 14 definite.

Claim 15, and dependent claims 16 and 17, have been limited to immunological "protein", as suggested in the Office Action.

Claim 24 has been amended to correct the antecedent basis. Claim 24 is distinguished from claim 1 because claim 1 claims a retroviral vector, and claim 24 claims a retroviral particle comprising the vector.

Claims 30 and 46 have been cancelled, rendering the rejection of those claims moot.

The term "tile" in claim 47 was a typographical error, which has been corrected. Language has also been added to clarify the position of the elements, particularly the NOIs, with respect to one another. Claim 47 no longer recites "the packaged pro-viral vector", obviating the rejection on that basis. In addition, the claim has been amended so that the step of packaging results in a viral particle, as suggested in the Office Action. Part (c) has also been rewritten to clarify the reverse transcription aspect. As is depicted in Figure 27c, the method of claim 47 actually results in two splice donor sites - the original 3' SD and the 5' SD that is the result of reverse transcription. This is well described in the specification, and presented definitely in claim 47.

Claim 48 has been cancelled, obviating the rejection.

The dependency of claim 50, from which claim 51 depends, has been changed, such that claim 51 is no longer limited to a first NOI that is expressed.

Claim 52 has been cancelled, obviating the rejection.

It is respectfully submitted that, since claim 55 recites "further comprises" with respect to the pro-vector of claim 47, it is clear that the transcriptional control sequence does not encompass the LTRs, SD and SA, but is in addition to the other components. The position of the transcriptional control sequence can be at any location upstream of the SD, as is recited in claim 55 and further defined by dependent claims 60-62, wherein the sequence can be internal or in either LTR.

Claim 56 has been cancelled, rendering its rejection moot.

As the amendment to claim 57(d) makes clear, the 3' LTR is not considered an NOI, but is located downstream of the NOI.

Claim 58 is not redundant, as it claims a retroviral particle, while claim 57 claims a retroviral vector. Nevertheless, claim 58 has been amended to simplify the language.

Accordingly, reconsideration and withdrawal of the rejections under 35 U.S.C. §112, second paragraph, are requested.

CONCLUSION

In view of the amendments and remarks herewith, the application is believed to be in condition for allowance. Early and favorable reconsideration of the application, reconsideration and withdrawal of the rejections of the application, and prompt issuance of a Notice of Allowance, are earnestly solicited.

Respectfully submitted,

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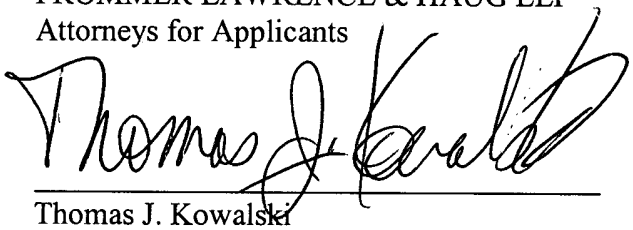
By: 

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